Design of new aggregates for catalysis

Tosi, Filippo

DOI:
10.33612/diss.107814277

Chapter 7

An Atom Efficient Synthesis of Tamoxifen

ABSTRACT: The direct carbolithiation of diphenylacetylenes and their cross-coupling procedure is presented taking advantage of the intermediate alkenyllithium reagents. Employing our recently discovered highly active palladium nanoparticle based catalyst (Chapter 6), we were able to couple an alkenyllithium reagent with high (*Z/E*) selectivity (10:1) and good yield to give breast cancer drug Tamoxifen in just 2 steps from commercially available starting materials and with excellent atom economy and reaction mass efficiency.

Part of this chapter was published as: D. Heijnen,† M van Zuylen,† F. Tosi,† B. L. Feringa *Org. Biomol. Chem.* **2019**, *17*, 2315–2320.

†These authors contributed equally.

7.1 Introduction

The continuous improvement of synthetic routes towards medicinal relevant and/or biologically active compounds has drawn the attention of synthetic chemists for decades.[1–5] In order to reduce waste and increase yields and cost efficiency or to simplify the procedures towards relevant structures, transition metal catalysis has been a game changer to the field.[6–9] Since the emergence of the Suzuki (B), Stille (Sn), Negishi (Zn) and Hiyama-Denmark (Si) reactions, the trend in cross-coupling methodology[10] has been to transmetallate highly polar (but straightforward to synthesize) organometallic reagents (RMgX, RLi) to softer nucleophiles in order to gain stability, functional group tolerance and reduce the overall sensitivity of the reaction. Despite their major role in our modern synthetic toolbox, drawbacks of these additional synthetic steps are longer reaction times, the production of stoichiometric (sometimes toxic) waste, and a decrease in cost efficiency.[11] Nonetheless, the direct coupling of organometallic reagents arising from a deprotonation or umpolung reaction has shown great advances in recent years.[6,7,12–23] Since these reagents have an intrinsically higher reactivity, the corresponding cross-coupling reactions generally require shorter reaction time, and can be performed at significantly lower temperatures.[24] As part of our effort to expand the synthetic application of our recently reported organolithium cross-coupling reactions,[12–14,19,21,22] we envisioned the direct carbolithation-cross-coupling to be a very valuable alternative. The carbolithiation of (diphenyl)acetylenes has been well-studied and has led to several useful applications in the field of synthetic organic chemistry.[25–30] The quenching of the formed nucleophilic sp^2 vinyllithium reagent with an electrophile provides a direct approach to substituted diarylalkenes (stilbenes). Transmetallation of such anions to magnesium, boron, zinc or even aluminum yields an active cross-coupling partner, but drastically lowers the atom economy and E-factor.[31–34] The direct cross-coupling of the formed organolithium reagent is therefore a highly desired synthetic shortcut, but remains unreported to the best of our knowledge. Tetrasubstituted alkenes and triphenylethylenes in particular, i.e. Tamoxifen, make up a class of highly potent and valuable drugs with (potential) application in the treatment of a variety of conditions, including (breast) cancer, dyspareunia and osteoporosis (Figure 7.1).[35] Structural variations on the triphenylethylene scaffold are found in the alkyl-ether substituent (mostly consisting of an amine, shown in blue), para phenylene functionality (shown in red) as well as in the alkyl fragment (shown in green) on the central alkene.

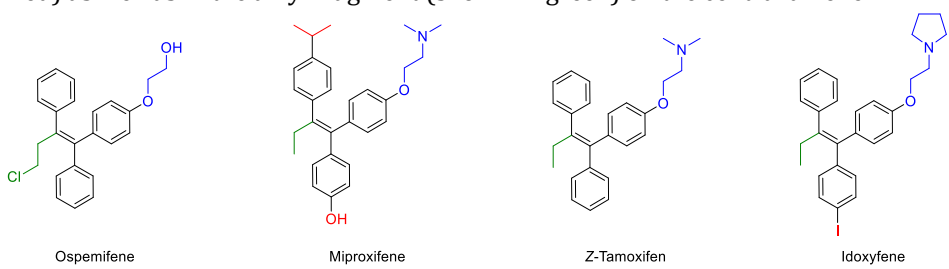


Figure 7.1: Examples of members of the triphenylethylene family of drugs.

Because of its medicinal importance, a plethora of syntheses have been described for (*Z*)-Tamoxifen (Figure 7.2).[36–58] McMurry coupling of two ketones is a well-established method for the synthesis of (hindered) alkenes, and as such has proven capable of constructing the alkene fragment in Tamoxifen with reagents **1** and **2**.[55] Alternatively, 1,2-addition to ketone **3** with Grignard reagent **4** followed by elimination yields the alkene is a valuable option, however it is common that both isomers (*E/Z*) are isolated *via* this approach.[53,58] Transmetallation of the lithium intermediate that is the product of carbolithation of the corresponding acetylene yields the alkenyl-boronic acid/ester, or organozinc reagent **5**.[54,56] The cross-coupling of these reagents with bromide **6** provides a viable route towards the final drug. The transmetallation, however, generates extra synthetic steps and/or stoichiometric waste. We therefore reasoned that the direct coupling of the alkenyllithium reagent **7**, that is obtained upon carbolithiation of diphenylacetylene, would be an important atom efficient alternative to these methods.

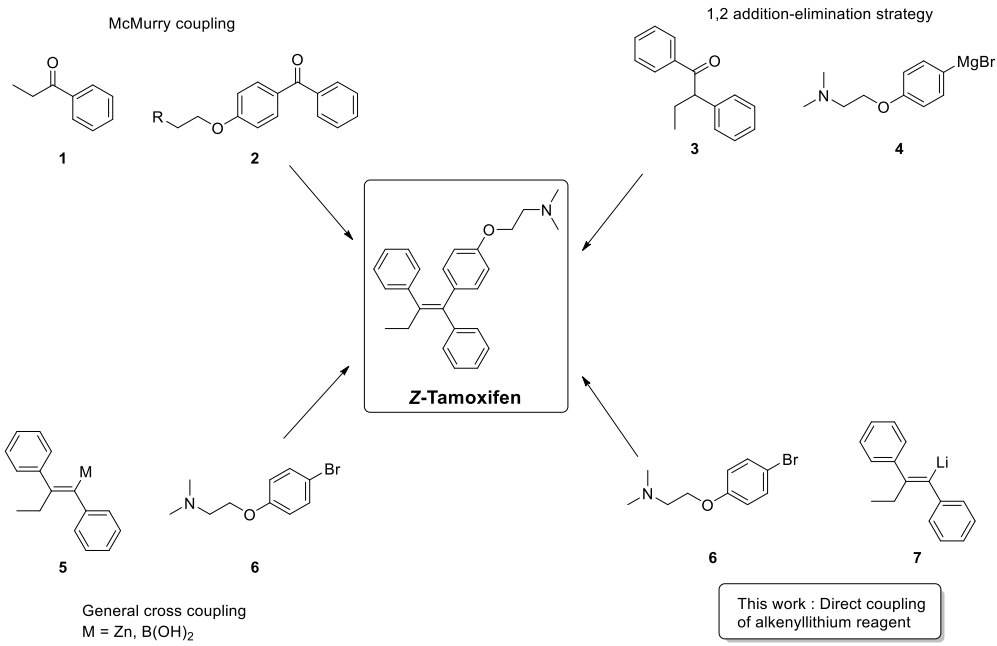
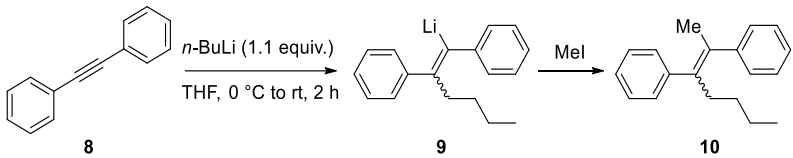


Figure 7.2: Synthetic approaches to (*Z*)-Tamoxifen.

7.2 Carbolithiation Optimization

In order to optimize the sequential synthetic steps, the carbolithiation of acetylene **8** was optimized separately, and the product **10** resulting from a MeI quench was subjected to GCMS analysis (Table 7.1). With high selectivity for the (*Z*)-alkene for several solvents and solvent mixtures investigated, we were trying to avoid

the use of THF (Table 7.1, Entry 1) due to expected difficulties in the cross-coupling step arising from unwanted side reactions, such as lithium-halogen exchange.[11–14,17,19–22] However, toluene/TMEDA mixtures (Entry 2) or other ethereal solvents (Entry 3 to 5) did not prove equally efficient as reaction medium compared to THF due to a lower extent of lithiation and an increased amount of the (*E*)-alkene. Attempts to minimize waste production by neat carbolithiation (except for the solvent of the *n*-BuLi solution) resulted in mere recovery of the starting material (Entry 6). Reducing the amount of THF by using a THF-toluene mixture resulted in incomplete conversion to the carbolithiated intermediate (Entry 7). Despite the attempts to omit THF as the solvent, we found significantly better results for the carbolithiation in its presence, and therefore decided to use it as the solvent for further optimization.

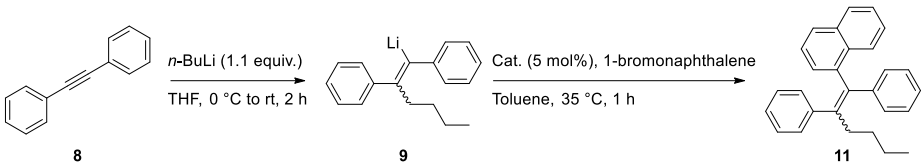


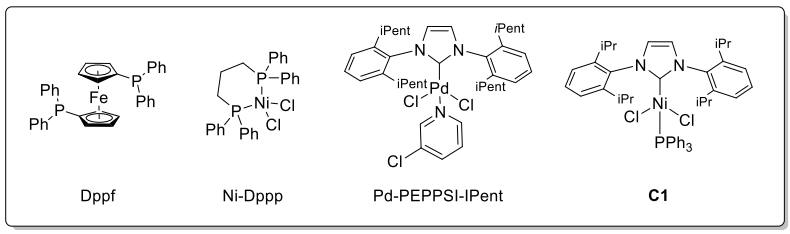
Entry	*Solvent*	*1 h Conv.*[a]	*2 h Conv.*[a]	*Selectivity*[b]
1	THF	91%	91%	96%
2	Toluene/TMEDA[c]	32%	32%	75%
3	2-Me-THF	52%	70%	99%
4	MTBE	0%	6%	-
5	Ether	0%	4%	-
6	Neat	0%	0%	-
7	Toluene/THF 3:1	48%	65%	96%

Table 7.1: Optimization of carbolithiation of **8**. Reaction conditions: 1.1 equiv. of *n*-BuLi was added dropwise to a stirred solution of **8** (0.9 M in THF) at 0 °C. At the end of the addition the reaction mixture was quickly allowed to warm to rt and left stirring for 2 h before 1 equiv. of MeI was added. a) As determined by GCMS analysis after MeI quench; b) (*Z*/*E*) selectivity determined by GCMS analysis; c) 1 equiv. of TMEDA.

7.3 Reaction Optimization

Having established the optimized conditions for the carbolithiation, the cross-coupling with 1-bromonaphthalene provided the test reaction in the pursuit for the best catalyst. Our oxygen activated palladium nanoparticle catalytic system[14] presented in Chapter 6 proved to be highly active in the coupling of alkenyllithium **9** and arylbromides (Table 7.2, Entry 1), being only slightly outperformed by the commercial Pd-PEPPSI-Ipent complex (Entry 4).

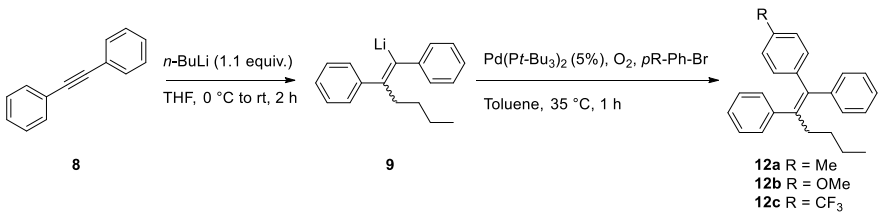




Entry	*Cat. (5 mol%)*	*Conversion to **11**[a]*
1	$Pd(Pt\text{-}Bu_3)_2 + O_2$	82% (68% yield)
2	$PdCl_2$-dppf	-
3	$NiCl_2$-dppp	-
4	PEPPSI-IPent	88%
5	**C1**	51%

Table 7.2: Optimization of cross-coupling of **9** with 1-bromonaphthalene. Reaction conditions: 2 equiv. of alkenyllithium reagent was added over 20 min to a stirred solution of arylbromide and (pre-oxidized) catalyst in toluene at 35°C. a) As determined by GCMS analysis, (*Z*/*E*) > 9:1.

Nickel and palladium bisphosphine complexes (Pd-dppf and Ni-dppp) did not show conversion to the desired product (Entry 2 and 3), but the nickel carbene complex **C1**[13] did provide the triarylethylene target **11** (Entry 5), albeit in reduced yield. In order to see if this cross-coupling methodology could be applicable for the cross-coupling of other arylbromides, we decided to test further few substrates (Table 7.3). The cross-coupling methodology proceeds smoothly with both electron-rich aryl bromides (R = Me, OMe, Entry 1 and 2), as well as electron-poor substrates (R = CF_3, Entry 3).

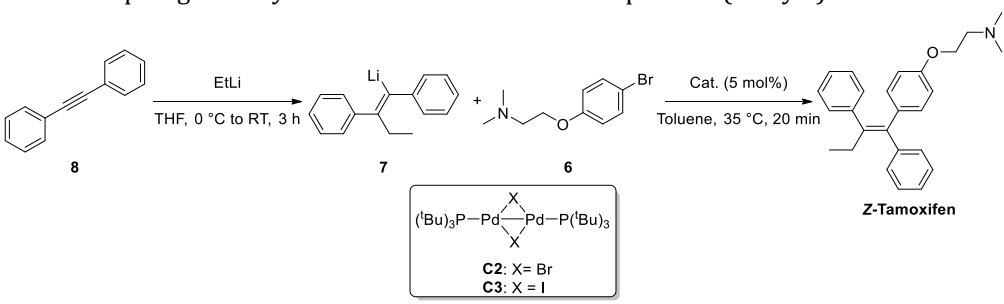


Entry	*R*	*Product*	*Yield of **12**[a]*
1	Me	**12a**	56%
2	OMe	**12b**	51%
3	CF_3	**12c**	68%

Table 7.3: Reaction scope of cross-coupling of **9** with different aryl bromides. Reaction conditions: 2 equiv. of alkenyllithium reagent was added over 20 min to a stirred solution of aryl bromide and (pre-oxidized) catalyst in toluene at 35°C. a) Isolated yield after column chromatography.

7.4 Tamoxifen Synthesis

Having tested a small variety of catalysts for the cross-coupling with different substrates, the optimized conditions were employed to synthesize the desired pharmaceutical (*Z*)-Tamoxifen *via* our new methodology. Changing the nucleophile for the acetylene carbolithiation from *n*-butyllithium to ethyllithium gave identical results albeit with a slightly longer reaction time. We were pleased to see that the oxygenated Pd(P*t*-Bu$_3$)$_2$ catalyst gave (*Z*)-Tamoxifen in only slightly lower yield than with the naphthalene test substrate, but with very good (*Z*/*E*) selectivity (Table 7.4, Entry 1, (*Z*/*E*) > 9:1). Pursuing a cheaper catalyst, with a more abundant metal, the attempted nickel complex gave only small amounts of the desired product (Entry 2).

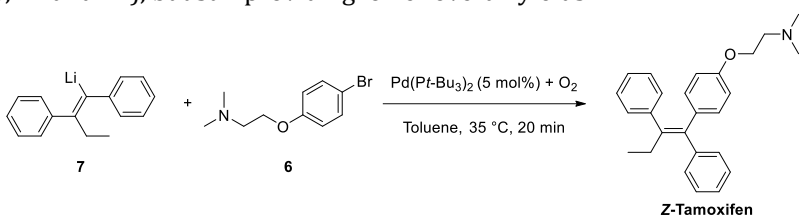


Entry	*Cat. (5 mol%)*	*NMR Yield*[a]
1	Pd(P*t*-Bu$_3$)$_2$ + O$_2$	50-65%[b]
2	**C1**	17%
3	PEPPSI-IPent	0%
4	Pd$_2$dba$_3$/Xphos	36%
5	**C2**[c]	60%
6	**C3**[c]	59%

Table 7.4: Synthesis of Tamoxifen, catalyst screening. Reaction conditions: 2 equiv. of alkenyllithium reagent was added over 20 min to a stirred solution of arylbromide **6** and (pre-oxidized) catalyst in toluene at 35°C. a) Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard, accompanied by <10% of (*E*)-Tamoxifen relative to (*Z*)-Tamoxifen; b) Isolated yield up to 57 %; c) 2.5 mol% of the Pd dimer was used.

Much to our surprise, our "working horse" catalyst Pd-PEPPSI Ipent[12,22] was completely inactive in the cross-coupling with the bromophenyl-aminoether electrophile **6** (Table 7.4, Entry 3), whereas it showed to be the most active catalyst with the previously tested 1-bromonaphthalene electrophile (Table 7.2, Entry 4). The chelating effect of the amino-ether moiety onto the metal center, overcrowding the palladium, might play a role making the catalyst inactive. Other dimeric palladium phosphine complexes (**C2**, **C3**) which have recently shown to be active in related cross-coupling reactions were also tested,[14,23] and were found to have very similar reactivity compared to the catalyst used in Entry 1. Being the cheapest of the three related structures (Entry 1, 5 and 6), we decided to proceed our investigation with the

bis(tri-*tert*-butylphosphine)palladium complex. The results of further optimization are shown in Table 7.5. Varying the temperature did not lead to increased yield (Entry 1 and 2) providing the temperature was kept above 30 °C, below which no conversion was observed. In an attempt to dissociate potential aggregates, and activate the organolithium reagent, TMEDA was added, but this resulted in a sharp decline in yield (Entry 3). The excess of organolithium reagent could be lowered to 1.3 equivalents without significant loss in yield (Entry 4). Further lowering of the catalyst loading (2.5 mol%) led to an inactive system, with no product formed (Entry 6 and 7). This complete deactivation of the catalyst at 2.5 mol% has not been observed before, and it is potentially attributed to the chelating effect of the aminoether moiety that is present in the substrate. An attempt to prevent the chelating effect of the aminoether side chain by means of addition of Lewis acids such as BF_3 or $MgCl_2$ did not prove beneficial for the reaction (Entry 8 and 9). To minimize waste caused by solvent, the reaction was performed in a minimal amount of solvent, at a 1 M concentration, which only led to a slight decrease in yield (Entry 10). Lower loadings of complexes **C2** and **C3** provided better conversion than our catalyst of choice at those concentrations (Entry 6, 11 and 12), but still providing lower overall yields.



Entry	*Modifications*[a]	*Yield*[b]
1	Temp 50°C	60
2	Temp 35°C	68
3	TMEDA (1 equiv.)	25
4	1.3 equiv. of **7**	65
5	10 % cat., 1.3 equiv. of **7**	65
6	2.5 % cat.	-
7	2.5 % cat.[c]	-
8	BF_3	-
9	$MgCl_2$	58
10	Concentrated (1 M)[d]	54
11	**C2**[e] 1.25 % cat.	14
12	**C3**[e] 1.25 % cat.	28

Table 7.5: Optimization of carbolithiation-cross-coupling sequence. a) Reaction conditions: 2 equiv. of alkenyllithium reagent was added over 20 min to a stirred solution of aryl bromide **6** and pre-oxidized catalyst in toluene at rt. b) Yield determined by ^{1}H NMR with 1,1,2,2-tetrachloroethane as internal standard; c) Different batch of catalyst; d) Initial concentration of arylbromide; e) the complexes **C2** and **C3** were used with the same Pd concentration as entries 6 and 7.

7.5 Reaction Mass Efficiency

Having a setup that produces this pharmaceutical compound in good yield and with minimal waste (LiBr being the only stoichiometric waste in the last step), we compared our procedure with other (recent) reported syntheses of Tamoxifen[25,26,36–58] focusing on atom economy and Reaction Mass Efficiency (RME).[34] Figure 7.3 shows a large range in atom economy (shown in blue) between different reported syntheses of Tamoxifen. The method described by Larock in 2005[51] is the closest to the reported route in this work in terms of atom economy (48 *vs.* 67%), but due to a large excess of some reagents it scores much lower on RME (shown in red).

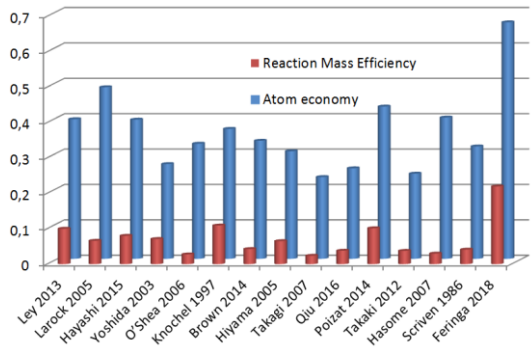


Figure 7.3: Atom economy and RME comparison for each reported Tamoxifen synthesis.

With our current setup, employing commercially available starting materials, a total atom economy of 0.67 is achieved, and the resulting RME (22%) is almost twice as high as that of the runner-up (Knochel 1997, 11%).[54] We believe that the currently reported methodology presents additional relevant advantages, since LiBr, NaCl and HCl are the only stoichiometrically produced waste sources, and the reaction can be performed at slightly elevated temperature in a minimal amount of solvent.

To establish the optimal isolation method, the synthesized (*Z*)-Tamoxifen was purified by means of crystallization, extraction, column chromatography and distillation. The excess organolithium reagent (protonated after reaction quenching, **12-H**) and the formed lithium bromide pose no difficulty in the separation from the product (Figure 7.4). Acid-base extraction or column chromatography were both suitable means to achieve purification.

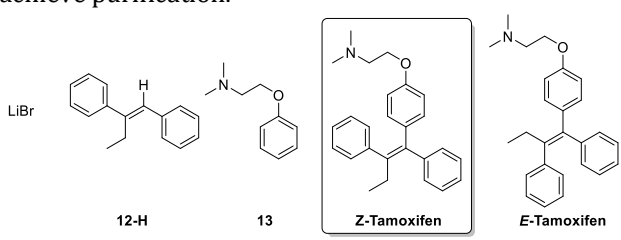


Figure 7.4: (*Z*)-Tamoxifen and side products.

The remaining impurity of dehalogenated starting material **13** exhibits near identical behavior compared to the product, but flash chromatography was able to yield the pure (*E/Z*)-Tamoxifen mixture. If desired, RP-preparative HPLC in water/ acetonitrile/TFA separates effectively the (*E*) from the (*Z*) isomer of the product.

7.6 Conclusions

In conclusion, the carbolithiation of diphenylacetylene and consecutive cross-coupling with the appropriate 4-bromo-dimethylamine-ethylether (**6**) yields (*Z*)-Tamoxifen with good (*Z/E*) selectivity (10:1) and with yields up to 65%. The reaction mixture was purified by flash chromatography to obtain the pure (*E/Z*)-Tamoxifen mixture. Further optimization could lead to a lowering of the catalyst loading and suppressing the lithium halogen exchange or *E-Z* isomerisation that lead to the undesired side products which have proven to be a challenge in the purification of this pharmaceutical. The method distinguishes itself from previously reported syntheses by its high atom economy, Reaction Mass Efficiency, non-toxic waste production, step count and ease of reaction setup. The organolithium cross-coupling is also an attractive strategy for the coupling of less reactive electrophiles (chlorides, fluorides and ethers)[13] and future studies might further enhance the efficiency towards triarylethylenes and related products.

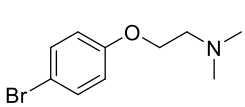
7.7 Contributions

This project was designed by dr. D. Heijnen and prof. dr. B. L. Feringa. The carbolithiation step and cross-coupling were optimized by M. van Zuylen under the supervision of F. Tosi and dr. D. Heijnen. Reproducibility and substrate scope were investigated by F. Tosi and dr. D. Heijnen.

7.8 Experimental Section

White colored Pd(P-*t*Bu$_3$)$_2$, was purchased from Strem chemicals and stored under nitrogen at -25 °C. Other metal complexes were purchased from Sigma and Strem chemicals and used as received.

7.9 Synthetic Procedures



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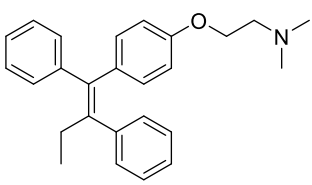
NaH (60%, 1.36 g, 34 mmol) was washed twice with dry hexane (5 mL) under a nitrogen atmosphere, suspended in dry THF (5 mL) and cooled in an ice bath. In a separate Schlenk flask, 4-bromophenol (3.0 g, 17 mmol) was dissolved in dry

THF (8 mL) and the solution was added dropwise to the NaH suspension. After the addition was complete, the ice bath was removed, 2-chloro-*N*,*N*-dimethylethylamine hydrochloride (2.4 g, 17 mmol) was added in portions and the reaction mixture was heated at 40 °C for 72 h. The reaction mixture was allowed to cool down to rt and the formed precipitate was filtered off. The filtrate was concentrated *in vacuo* and redissolved in EtOAc (50 mL), extracted with aq. 1 M HCl (3 x 50 mL), then neutralized with sat. aq. Na_2CO_3, extracted with EtOAc (100 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The product **6** (4.2 g, 56%) was obtained without further purification as a colorless liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 4.03 (t, J = 5.7 Hz, 2H), 2.72 (t, J = 5.7 Hz, 2H), 2.33 (s, 6H). *The spectral data was found in agreement with the literature*.[59]



***Z*-Tamoxifen**

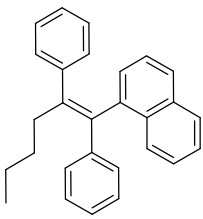
Preparation of lithio-stilbene: In a dry Schlenk flask (A) under a nitrogen atmosphere, diphenylacetylene (160 mg, 0.9 mmol) was dissolved in dry THF (1 mL) and cooled down to 0 °C. EtLi (0.5 M in Cyclohexane/Benzene, 1.85 mL, 0.93 mmol) was added dropwise, causing the reaction mixture to turn orange. The mixture was allowed to quickly warm to rt and left stirring for 3 h, during which the color changed to yellow and eventually light green. The resulting solution was diluted with dry toluene (2 mL) (*Solution A*).

Procedure for the cross-coupling: In a dry Schlenk flask (B) Pd(P-*t*Bu_3)$_2$ (15 mg, 0.030 mmol) was dissolved in dry toluene (2 mL) under a nitrogen atmosphere. Dry oxygen (12 mL) was bubbled through the mixture which was left stirring vigorously for 16 h, resulting in an intense red solution. Compound **2** (146.4 mg, 0.6 mmol) was dissolved in dry toluene (1 mL) and added to the mixture. Solution A (freshly prepared) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over Celite and concentrated *in vacuo*. The resulting liquid was dissolved in EtOAc (20 mL) and extracted four times with aq. 1 M HCl (30 mL). The aqueous layer was neutralized with Na_2CO_3 and extracted with EtOAc (4x50 mL). The organic layer was dried with Na_2SO_4* and concentrated *in vacuo*. The crude yield was determined by ^{1}H NMR analysis, using 1,1,2,2-tetrachloroethane as an internal standard (*in reference with the integration of the doublet signal at δ 6.56 ppm*). Purification by flash column chromatography (SiO_2, CH_2Cl_2/MeOH: 96:4) gave Tamoxifen ((*Z*/*E*): 10:1, 127 mg, 57 %) as a yellow semisolid.

Prep-HPLC purification: Purification by RP (C18 Denali) prep-HPLC (H_2O/CH_3CN/TFA: 50:49:1) on 15 mg of the (*E*/*Z*)-product gave pure (*Z*)-Tamoxifen; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.5 Hz, 2H), 7.25 (m, 4H), 6.76 (d, J = 8.8 Hz, 2H), 6.56 (d,

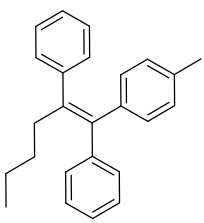
* *The use of $MgSO_4$ induces the formation of magnesium chelated complexes hampering the purification of the Tamoxifen product.*

J = 8.8 Hz, 2H), 3.92 (t, *J* = 5.8 Hz, 2H), 2.64 (t, *J* = 5.8 Hz, 2H), 2.46 (q, *J* = 7.4 Hz, 2H), 2.28 (s, 6H), 0.92 (t, *J* = 7.4 Hz, 3H). HRMS (ESI) *m/z*: $[M+1]^+$ Calcd for $C_{26}H_{30}N_1O_1$ 371.2322, Found 371.2326. *The spectral data was found in agreement with the literature.*[56]



11

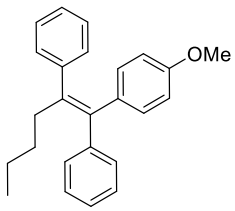
In a dry Schlenk flask (B) Pd(P*t*-Bu$_3$)$_2$ (13 mg, 15 μmol) was dissolved in dry toluene (2 mL) under a nitrogen atmosphere. Dry oxygen (6 mL) was bubbled through the mixture which was left stirring vigorously for 16 h, resulting in an intense red solution. 1-bromonaphtalene (104 mg, 0.501 mmol) was dissolved in dry toluene (0.5 mL) and added to the mixture. A (freshly prepared) solution of lithio-stilbene (as described above) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over Celite and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, Pentane) gave pure **11** (124 mg, 68%) as a white solid; (R_f: 0.85, Pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.04 (m, 1H), 7.69 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.43 – 7.15 (m, 10H), 7.12 – 7.02 (m, 2H), 6.98 – 6.91 (m, 2H), 2.75 (ddd, *J* = 13.4, 9.4, 6.4 Hz, 1H), 2.61 (ddd, *J* = 13.5, 9.3, 6.4 Hz, 1H), 1.56 – 1.43 (m, 2H), 1.42 – 1.29 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 143.3, 142.7, 142.6, 140.9, 137.3, 133.5, 132.1, 128.9, 128.7, 128.3, 128.1, 128.0, 127.3, 126.7, 126.5, 126.4, 126.0, 125.5, 125.2, 125.1, 34.9, 31.5, 22.9, 13.9.†



12a

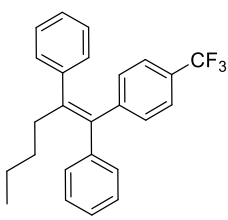
In a dry Schlenk flask (B) Pd(P*t*-Bu$_3$)$_2$ (7.7 mg, 15 μmol) was dissolved in dry toluene (1 mL) under a nitrogen atmosphere. Dry oxygen (6 mL) was bubbled through the mixture which was left stirring vigorously for 16 h, resulting in an intense red solution. p-Bromotoluene (51 mg, 0.31 mmol) was dissolved in dry toluene (0.5 mL) and added to the mixture. A (freshly prepared) solution of lithio-stilbene (as described above) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over Celite and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, Pentane) gave pure **12a** (55 mg, 56%) as a white solid; (R_f: 0.2, Pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.24 (m, 3H), 7.14 (m, 5H), 6.82 (d, J = 8.2 Hz, 2H), 6.67 (d, J = 8.2 Hz, 2H), 2.43 (m, 2H), 2.19 (s, 3H), 1.31 (m, 2H), 1.23 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 142.9, 140.7, 140.2, 139.0, 135.3, 130.8, 129.7, 129.6, 128.2, 128.2, 127.9, 126.6, 126.1, 35.9, 31.3, 22.9, 21.2, 14.0. *The spectral data was found in agreement with the literature.*[50]

† The presence of an extra ^{13}C signal is possibly due to the presence of a small amount of *E*-isomer of the product.



12b

In a dry Schlenk flask (B) Pd(P*t*-Bu$_3$)$_2$ (7.7 mg, 15 μmol) was dissolved in dry toluene (1 mL) under a nitrogen atmosphere. Dry oxygen (6 mL) was bubbled through the mixture which was left stirring vigorously for 16 h, resulting in an intense red solution. *p*-Bromoanisole (56 mg, 0.31 mmol) was dissolved in dry toluene (0.5 mL) and added to the mixture. A (freshly prepared) solution of lithio-stilbene (as described above) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over Celite and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, Pentane/CH_2Cl_2: 8:2) gave pure **12b** (53 mg, 51%) as a white solid; (R_f: 0.5, Pentane/CH_2Cl_2: 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.26 (m, 3H), 7.15 (m, 5H), 6.80 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 3.69 (s, 3H), 2.44 (m, 2H), 1.32 (m, 2H), 1.22 (m, 2H), 0.79 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 144.0, 142.9, 140.4, 138.6, 135.7, 132.0, 129.7, 129.7, 128.2, 128.0, 126.6, 126.1, 112.9, 55.1, 35.8, 31.3, 22.9, 14.0; HRMS (ESI) *m/z*: $[M+1]^+$ Calcd for $C_{25}H_{25}O_1$ 341.1899, Found 341.1898.



12c

In a dry Schlenk flask (B) Pd(P*t*-Bu$_3$)$_2$ (12.7 mg, 15 μmol) was dissolved in dry toluene (2 mL) under a nitrogen atmosphere. Dry oxygen (6 mL) was bubbled through the mixture which was left stirring vigorously for 16 h, resulting in an intense red solution. *P*-bromobenzotrifluoride (112.5 mg, 0.5 mmol) was dissolved in dry toluene (0.5 mL) and added to the mixture. A (freshly prepared) solution of lithio-stilbene (as described above) was added over the course of 20 min by means of a syringe pump. After the addition, the reaction mixture was quenched with 0.5 mL of MeOH, filtered over Celite and concentrated *in vacuo*. Purification by flash column chromatography (SiO_2, Pentane) gave **12c** (142 mg, 68 %) as a mixture with 10% of the impurity arising from protonation of compound **9**; (R_f: 0.9, Pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 2H), 7.40 – 7.14 (m, 13H)‡, 7.10 (dd, *J* = 7.9, 1.8 Hz, 2H), 6.99 (d, *J* = 8.1 Hz, 2H), 2.54 – 2.37 (m, 2H), 1.37 – 1.28 (m, 2H), 1.27 – 1.17 (m, 2H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR§ (101 MHz, $CDCl_3$) δ 146.8, 142.9, 142.7, 141.8, 137.7, 131.6, 130.9, 129.5, 129.4, 128.8, 128.3, 128.3, 128.2, 128.2, 128.0, 127.1, 126.9, 126.6, 126.6, 124.3, 124.3, 124.2, 123.3, 35.8, 31.0, 22.8, 13.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4.

7.10 References

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‡ Signal originating from product and identified impurity.

§ The amount of ^{13}C signal is due to the presence of the impurity arising from protonation of compound **9**, and the splitting due to coupling with the ^{19}F nucleus.

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